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Disease-a-Month

Meningitis

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Meningitis

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MENINGITIS IS KNOWN as a mortal infection. The diagnosis frequently evokes apprehension about epidemic illness, high case fatality rates and dread neurologic manifestations or sequelae. All these connotations have a basis in fact. Fortunately, progress in microbiology during the past three quarters of a century, and recently with respect to viruses, has greatly increased our understanding and ability to differentiate the meningitides. Concomitant advances in control of infectious diseases and the recent development of effective agents for the treatment of bacterial infections have permitted equally great accomplishments in the prevention and treatment of meningitis. Thus, within the past two decades one can trace the decline in case fatality rates of some types of bacterial

meningitis from more than 90% to less than 5%. Among infections, however, bacterial meningitis still accounts for a large number of deaths. As recently as World War II, meningococcal meningitis and meningococcemia were the greatest cause of death from infection (1).

With the availability of effective antibacterial agents, emphasis in meningitis has shifted toward the problem of early and accurate diagnosis. For many types of meningitis, this is now the weakest link in effective control. Improvement in this area will depend on the alertness of physicians to the possibility of meningitis, the availability and appropriate use of laboratory facilities and the judicious use of antibiotics for treatment.

As the urgency for major improvements in therapy has declined, new kinds of treatment have received less attention and there has been an increasing body of literature concerned with previously unknown and rare causes of meningitis. An appropriate review at this time must call attention to the increased recognition and perhaps increased frequency of the syndrome of aseptic meningitis. New viral etiologies have been discovered and the importance of other causes of the syndrome better documented. In this presentation, the attempt will be to obtain a panoramic view of the entire group of meningitides. Concepts of the disease will be given and particular attention paid to the practical clinical and laboratory means for the recognition, complete diagnosis, pathologic interpretation and management of meningitis.

PATHOGENESIS

The leptomeninges are susceptible to infection with a great variety of microorganisms including bacteria, spirochetes, viruses, rickettsiae, yeasts and other fungi. Anatomically, the pia and arachnoid are bathed with a fluid that can serve as a nutrient medium for extracellular parasites, and which is relatively free of plasma antibody and perhaps other protective proteins.

The sources and routes of infection are many. Meningitis may be initiated by a hematogenous process which is part of a generalized infection as with meningococcemia, or local infections in a particular organ, such as pneumonia or pyelonephritis. Its origin may be metastatic, arising from septic emboli as a complication of chronic pulmonary infection, subacute bacterial endocarditis or osteomyelitis. This last group is not en-

countered frequently, since a massive dose of organisms is required via the blood stream to produce a generalized meningitis.

Another important source of meningeal infection is otitis media, mastoiditis and infection of the paranasal sinuses. These infections provide a route for continuous seeding of the leptomeninges with organisms, which ultimately overwhelm the meningeal defenses. It is difficult to establish the exact route of spread of infection in individual cases. It is believed that the infection spreads through bone by contiguity and along blood vessels to the underlying dura where it produces granulations. The leptomeninges are probably infected via a retrograde thrombophlebitis of veins that pass between the leptomeninges and dura, or sometimes by thrombophlebitis of the dural sinuses.

Penetrating head wounds resulting in direct contamination of the meninges are an important cause of meningitis among military personnel. In civilian life, trauma leads to meningitis through fractures of the base of the skull, the cribriform plate, or frontal bone, which provides infections of the paranasal sinuses direct access to the meninges. Persistent traumatic tears of the frontal dura and leptomeninges produce cerebrospinal fluid rhinorrhea which provides a pathway by which organisms can spread reversely from the nasal cavity intracranially.

The cerebrospinal fluid itself may serve as the source of meningeal infection, if organisms are introduced by lumbar puncture or by some other diagnostic procedure. In this connection, the work of Rich (2) indicates that in tuberculous meningitis the usual mode of infection is constant seeding of the cerebrospinal fluid with organisms from small meningeal tuberculomas or tuberculomas in subpial or subependymal locations.

EPIDEMIOLOGY

Meningitis is often an epidemic illness which involves a certain population group or community with dramatic onset of acute illness. Also, sporadic cases of meningitis of nearly every etiology continue to appear between epidemic outbreaks. Classic epidemics of cerebrospinal meningitis probably caused by the meningococcus were described by Vieusseux and North early in the nineteenth century (3). Contact with infected pa-

tients and person-to-person transfer among healthy carriers are the most important modes of transmission of the meningococcus. Epidemics caused by some of the viruses that infect the meninges and central nervous system also are spread either directly or indirectly from person to person via the respiratory or gastrointestinal route.

In some forms of meningitis, such as that caused by leptospira, there is no evidence for person-to-person transmission, but often there is a uniform type of exposure, such as immersion in stagnant water or contact with a rat-infested environment, which can be identified as the source of infection.

Other forms of meningitis in which there is no evidence for person-to-person spread, such as that caused by *Cryptococcus neoformans*, can be considered almost entirely dependent on specific factors that render the host susceptible to infection. Thus, in considering patients with meningitis, the epidemiologic factors of age, sex, season, ecology, prior health status of the host and previous treatment of the patient are important considerations which can be of great help in suggesting the accurate diagnosis among the meningitides.

Age

Age is one of the most important considerations in the cause and prognosis of meningitis. In this respect, the important divisions are the neonatal period, consisting of the first 2 to 6 weeks, early infancy to around age 3, from 3 to 40, and adults past 40.

Peak incidence of the most common types of bacterial meningitis is during the period from 1 month to 1 year (4). Approximately one half of the cases of meningitis in the pediatric age group occur during this period. Infections during the first month of life also are common and account for about one quarter of pediatric cases of meningitis. Neonatal meningitis is predominantly of different etiology from those that occur in childhood. Passive transfer of maternal antibody to the fetus is an effective endowment for the prevention of infection with *H. influenzae*, several types of pneumococci and viruses; also, when the mother is immune, for the meningococcus and some of the less frequent causes of meningitis. Appreciable resistance does not seem to be transferred against the coliform organisms, staphylococci and certain groups of streptococci. These common inhabitants of the birth canal and adjacent

structures are the principal causes of meningitis in the newborn. Two thirds of cases caused by *E. coli* occur in this period. Just as there is transplacental passage of antibody, there is occasional intrauterine initiation of meningeal infection, especially with a virus (5).

Beyond the first few weeks of life and during the first few years, *H. influenzae* is the most common single cause of meningitis. During this high-incidence period, meningococcal, pneumococcal and tuberculous meningitis also attain their greatest morbidity. Beyond age 2 or 3, the occurrence of bacterial meningitis from all causes declines markedly. *H. influenzae* especially is less frequent. The attack rate from meningococcus, pneumococcus and tuberculosis declines more slowly, and cases continue to occur throughout the entire age span, although one half or more occur before age 10.

During childhood and early adulthood, the incidence of viral meningoencephalitis, principally caused by lymphocytic choriomeningitis, mumps, herpes, poliomyelitis, Coxsackie and ECHO viruses, reaches its zenith. Approximately three fourths of these cases occur before age 20. Leptospirosis also is most common in this age group.

Beyond age 40, pneumococcal, staphylococcal and tuberculous meningitis continue to occur and again become the most common types. Influenzal meningitis is extremely rare. Only 31 adult cases have been reported in the literature (6). Meningococcal meningitis is markedly less frequent than in younger groups, and meningitis caused by a variety of uncommon microorganisms may be observed.

Sex

The predisposition of people to meningitis because of sex per se is difficult to distinguish from the occupational and social behavior patterns characteristic of each sex. Because of recurrent mobilization of military forces, meningococcal meningitis has shown a marked predominance among males. In a civilian outbreak, however, cases among males also were observed to predominate in a ratio of about 2 to 1 (7). Pneumococcal infections of all types, including meningitis, are more frequent in males. Males also predominate among cases of Nocardia infection of the central nervous system and meninges (8). In the newborn, meningitis caused principally by coliform bacilli is more common among males.

Among viral infections, the incidence and susceptibility of females to poliomyelitis varies in different periods of the menstrual cycle or pregnancy (9). In mumps meningitis, males predominate more than 2 to 1 (10). Males and females are equally susceptible to lymphocytic choriomeningitis and Coxsackie viruses.

Season

The seasonal fluctuation of many infections is a curious phenomenon. It can be demonstrated for most, if not all, etiologic agents in meningitis that have caused enough cases to permit such a study. Infections with the meningococcus occur with a seasonal cyclic variation both during and between epidemic periods. In the temperate zones, March and April are the months of peak occurrence. Clinical infections are infrequent during summer and fall months. Approximately every 8 or 10 years, a major epidemic wave of meningococcal infection has occurred. The most recent of these were in 1952-53 and 1942-44. Influenzal, pneumococcal and tuberculous meningitis are all most prevalent during winter and spring months.

Viral meningitides, in general, are more common during late summer and early fall when they may reach epidemic proportions. Infections with lymphocytic choriomeningitis and mumps, however, tend to occur later in winter and spring. From year to year there is great variation in the over-all case attack rates and in the prevalence of specific viruses. Epidemic waves of mumps infections occur in winter and spring months about every 8 years and, prior to the widespread use of vaccine, epidemic cycles of poliomyelitis occurred during summer months every 3-5 years.

Ecology

Meningitis is world-wide in occurrence, with members of all races affected. Most bacterial and viral types that occur commonly in the temperate climate also occur in other parts of the world with similar cyclic epidemic waves. Seasons of peak incidence differ, however, as does age susceptibility and relative prevalence of different kinds of meningitis.

Crowding in urban areas is an ecologic factor that affects the attack rates for different types of meningitis. Since World War II the rate of meningococcal infections has continued to

be unusually high among children of some countries, owing to the degradation of living quarters. The ratios are highest among the poorer and lower-middle-class families. The same prevalence among persons of different economic classes also has been reported for some types of viral meningoencephalitis.

Microorganisms of the genus leptospira and listeria and the lymphocytic choriomeningitis virus are causes of meningitis in man, which have a rather extensive animal reservoir and are primarily infections of certain domestic and wild animals. Salmonella, anthrax, tularemia and brucella, which are occasional causes of meningitis, also are largely infections of animals that may be transmitted to man usually as a systemic infection. In most instances, human infections of these types are acquired by direct contact with infectious material, but in some instances an arthropod vector has been suggested or shown.

Several species of leptospira cause human infection. The importance of rats in the transmission of *Lept. icterohaemorrhagiae* has long been known. *Lept. pomona* and *Lept. canicola* are common infections of cattle and hogs; the latter is widespread among dogs. Contact or immersion of the host in water contaminated by excreta of infected animals is a common epidemiologic feature of these cases.

Health Status of Host

Some hematologic diseases seem to increase the susceptibility of the subjects to meningitis from various, often unusual, causes. Approximately 10% of cryptococcal infections occur among patients who have a lymphoma, especially Hodgkin's disease (11). Others have diabetes or tuberculosis which might be related to their susceptibility. Prolonged treatment with adrenal cortical steroids may be an important factor in the altered susceptibility of some patients. Hypogammaglobulinemia may be an infrequent factor contributing to the development of bacterial meningitis. Among patients with sickle-cell hemoglobin, salmonella infections including meningitis are more common than normal.

Development of meningitis secondary to focal infections was noted in the section on Pathogenesis. People suffering from focal infections of the middle ear or paranasal sinuses, pneumonia, endocarditis, chronic urinary-tract infections, bronchiectasis and septic thrombophlebitis are susceptible to

meningeal infection derived from these sources. Focal infection and trauma are prominent factors among adult cases of meningitis caused by gram-positive cocci or coliform organisms.

CLINICAL SYNDROMES OF MENINGITIS

Patients with meningitis present a variety of clinical syndromes. Even patients infected with a single agent can differ markedly one from another. Symptoms of meningitis may be so meager and nonspecific that the clinical diagnosis can only be a suspicion. Some types of meningitis, however, have certain clinical features, such as the blotchy petechial rash of meningococcemia, that permit an accurate etiologic diagnosis on clinical grounds alone. More often the clinical diagnosis of meningitis implies one or another of several possible etiologic agents. The differential diagnosis can be narrowed by a careful clinical history, with attention to epidemiologic factors just discussed and to thorough examination of the patient. Finally, the proper collection of specimens of CSF and blood for laboratory examinations is necessary to substantiate a specific clinical diagnosis.

A general classification which will serve as a basis for discussion of the usual clinical syndromes observed among patients with meningitis follows. Only comments on the general clinical features will be given in this section. Neurologic examination of the patient, progression of pathologic changes and characteristics of CSF with different kinds of infection will be considered separately.

Clinical Syndromes

- Acute purulent meningitis
  - Primary meningitis (cerebrospinal fever)
  - Secondary meningitis (otitic, traumatic, embolic meningitis)
- Acute aseptic meningitis
  - Acute lymphocytic meningitis
  - Epidemic meningoencephalitis
- Subacute and chronic meningitis
  - Tuberculous
  - Nontuberculous
- Meningismus
- Serous meningitis (toxic meningitis)
- Parameningeal infections and tumors (sympathetic meningitis)

Each of these clinical syndromes has several etiologic causes that may be impossible to distinguish without laboratory aid. In clinical evaluation of the illness and management of the patient, such a categorization can be of assistance, especially in indicating the need and urgency for specific treatment or special diagnostic procedures.

Acute Purulent Meningitis

The clinical syndrome of purulent meningitis, whatever the bacterial etiology, is quite similar and usually acute or subacute. Principal differences are in age, prodromata, primary illnesses or other antecedent history of the patient. It is important to emphasize that the clinical picture in infants may be considerably different from that in children and adults. Fever, fretfulness and rejection of feedings may be the only manifestations of meningeal infection during the first year of life, although cyanosis, respiratory irregularity and some signs of increased intracranial pressure also are common. Among children and adults fever, headache, vomiting, disturbances in the state of consciousness and nuchal rigidity are the hallmarks of acute purulent meningitis. The syndrome may appear as a primary or secondary infection of the meninges, and this aspect has some relationship to the bacterial etiology.

Primary purulent meningitis.—*Meningococcal meningitis* is the classic prototype of primary bacterial meningitis (3, 12). A mild prodromal illness occurs in about one half of patients. This consists of common respiratory symptoms with mild pharyngitis, rhinitis or coryza. Herpes simplex is often present and may alert the physician to the possibility of a meningococcal infection. Malaise, general aching, low-grade fever, chilliness, headache and apathy, or listlessness, may characterize this stage of the illness which usually is brief.

More often the onset of meningococcal meningitis is abrupt, with fever and severe, persistent headache, especially in the occipital area. Vomiting often is projectile. Chills or chilliness with joint and muscle pains are characteristic of meningococcemia, which is an integral part of the illness. At first patients are restless or show delirium. Convulsions occur in about one half of cases under age 5, and approximately 20% above that age. Stupor and coma develop as the infection progresses. Temperature is generally in the range of 102F., but extreme

elevation of temperature may occur. Photophobia can be striking. Abnormal eye signs occur in only a small proportion, 5 or 6%, of patients with meningococcal meningitis. Papilledema is not present in uncomplicated primary bacterial meningitis.

The characteristic purpuric rash appears in more than half of the patients. Individual petechiae range to about 1 cm. in diameter and often coalesce into larger ecchymotic lesions. They may have a purplish hue, and do not fade with pressure; sometimes they show central necrosis. An occasional patient may have an erythematous maculopapular eruption. The lateral aspects of the trunk, the limbs, mucous membranes and retina often show these lesions. Although such a rash is not pathognomonic of meningococcal infection, the odds are overwhelmingly in favor of this diagnosis.

Biot's respiration, or "meningitic" breathing, consists of irregularity both in rate and depth of respiratory effort (13). Frequent sighs may be interposed with the irregular breathing. It is an omen for guarded prognosis.

Leukocytosis of 10,000 to 20,000 cells per mm^3. can be expected. Transient microscopic hematuria sometimes is observed. Stained smears of fluid aspirated from the purpuric skin lesions contain meningococci. Blood cultures are positive in a high proportion of patients.

The Waterhouse-Friderichsen syndrome is a fulminating form of meningococcal infection that may occur with or without meningitis. Space does not permit its discussion except to note the principal characteristics, which are sudden onset of peripheral-vascular collapse, prostration, cyanosis and purpuric rash.

Hemophilus influenzae meningitis is a primary disease of the meninges among infants and children (4, 14). Cases that occur among adults are ordinarily secondary to sinusitis, otitis, operations or accidental trauma to the head. The clinical picture resembles that described for meningococcal meningitis. A purpuric skin rash occurs rarely. Unexplained anemia may accompany meningitis caused by *H. influenzae* (15).

SECONDARY PURULENT MENINGITIS (otitic meningitis, posttraumatic meningitis or embolic meningitis).—*Pneumococcal meningitis* is secondary to acute sinusitis, otitis or infections of the eye, in one third to one half of cases. Another one quarter to one third are associated with lobar pneumonia, other respiratory infections or endocarditis, and approximately the same proportions follow skull fractures, cranial operations or

abnormalities. Among the latter group, recurrent bouts of pneumococcal meningitis may occur. The clinical features are those of acute meningitis modified by the primary illness. Skin rash is rare in the absence of endocarditis. Bacteremia is present in more than one half of patients.

Streptococcal and staphylococcal meningitis also are usually secondary meningeal infections. They occur in the newborn and sporadically in patients of all ages. Respiratory infections and omphalitis may serve as the portal of entry for the former. Furuncles, infected cutaneous lesions, and head trauma are the most common predisposing lesions in staphylococcal meningitis. Onset of meningitis is usually abrupt and severe, and it can develop from lesions considered clinically insignificant as well as with severe local infections.

Colon bacillus meningitis usually occurs in the newborn infant or subsequent to head injury or focal infection in the adult. The presence of a congenital meningocele or sinus tract predisposes an infant to meningeal infection, and search for such a lesion in a patient with colon bacillus meningitis will sometimes be rewarded. In the adult, urinary infection could be the source of meningitis with the colon bacillus. Onset of symptoms may be more insidious than with the preceding types of purulent meningitis and the clinical course subacute or drawn out.

Other bacterial species such as *Aerobacter aerogenes* (Friedländer's bacillus), *Pseudomonas aeruginosa*, Salmonella species, Bacteroides and some less common organisms, such as those of the genera Brucella, Pasteurella, anthrax, Listeria, Nocardia and others may produce acute purulent meningitis. In most cases, there is a primary lesion other than meningitis but, on occasion, such lesions are absent or unrecognized and patients present the clinical features of primary purulent meningitis. Subacute illness and recurrent relapses are likely to occur with meningitis caused by gram-negative bacilli, but sometimes the disease is fulminating. Focal infections and debilitating diseases are common predisposing conditions.

Acute Aseptic Meningitis

The syndrome of acute aseptic meningitis was defined by Wallgren in 1925 (16). It was designated as an acute, nonbacterial meningitis with a short, benign course, in patients without other focal infections, and which occurred at a time

when epidemic meningitis was absent from the community. It is now known that the syndrome can be simulated by numerous etiologic agents, many of them still unidentified. The clinical differentiation of the specific etiology of such an illness may be impossible.

ACUTE LYMPHOCYTIC MENINGITIS.—Brief consideration here will be given only to the clinical features of some common causes of the syndrome of lymphocytic meningitis likely to occur as sporadic cases. These include lymphocytic choriomeningitis, mumps, herpes simplex and leptospirosis. An excellent study on the occurrence of aseptic meningitis caused by these agents among military personnel and their dependents has been published (17).

Lymphocytic choriomeningitis classically develops in 2 phases. The first is an influenza-like illness which precedes the meningitic phase by 1-3 weeks. This aspect of the illness goes unnoticed in about one half of patients, whereas about one third have a clinical prodromal illness of moderate severity. The first phase of the illness may continue until it becomes overshadowed by meningitis, or the patient may recover for a few days before the onset of meningitis. Occasionally there are recurrent waves of illness. Headache, fever and stiff neck manifest the onset of meningitis. The patient is usually alert, and significant neurologic abnormalities are infrequent.

Mumps meningitis is perhaps the most frequent single recognized cause of clinical aseptic meningitis among young males (10, 17, 18). In most cases, involvement of the central nervous system follows a few days after development of parotitis. Sometimes the meningitis precedes salivary gland involvement or develops in the absence of overt infection of the salivary glands. Patients with mumps meningitis have the symptoms and signs characteristic of aseptic meningeal inflammation, with few or no distinctive features except parotitis or orchitis. Abnormal neurologic signs are usually minor and transient.

Herpes simplex meningitis is generally assumed to be a primary infection. Until recently most of the recognized cases occurred in early infancy and were diagnosed only at autopsy. It now appears that herpes simplex is the etiologic agent in 2-7% of cases of acute aseptic meningitis (17). The clinical illness is likely to be severe and associated with abnormal neurologic signs as well as evidence of meningitis. Mucocutaneous herpes are not present.

Leptospiral meningitis may be caused by strains of several serogroups of leptospira. *Lept. canicola* and *Lept. pomona*, especially, produce the typical clinical features of primary acute aseptic meningitis. Immersion or close contact with infected excreta or contaminated water is usually in the history. A prodromal, febrile illness may occur during the week or two before the onset of meningitis. Conjunctivitis might be a distinctive clue in leptospiral meningitis, and frank chills occur more frequently than with viral infections. Although meningitis is part of the clinical picture of infection with *L. icterohaemorrhagiae* (Weil's disease) the patient rarely, if ever, presents the syndrome of acute aseptic meningitis.

Other causes of the syndrome are being added rapidly. In addition to the common causes just noted, acute aseptic meningitis may occur as a part or even the prominent picture in patients with infectious mononucleosis, primary atypical pneumonia, lymphopathia venereum, rubeola, varicella and cat-scratch disease. Also, it may be caused by the group of neurotropic, Coxsackie and enteric orphan viruses considered herewith, as well as by the encephalitis and encephalomyocarditis viruses; by tuberculosis, cryptococci, actinomycosis and syphilis, which usually cause subacute or chronic meningitis; and by typhoid, Brucella, tularemia and Nocardia, which may in some instances, cause purulent meningitis. Helminthic infestation and undoubtedly many other microorganisms are rare causes of aseptic meningitis.

Additional perplexity in the clinical distinction of this syndrome is the difficulty created by inadequate antibiotic treatment of unrecognized purulent meningitis. Failure of recognition includes both lack of suspicion from the clinical examination and administration of antibiotics to patients with febrile illnesses as a therapeutic test before attempting a complete diagnosis. These patients may appear to have aseptic meningitis or one of the subacute or chronic meningitides.

EPIDEMIC MENINGOENCEPHALITIS (abortive poliomyelitis, epidemic aseptic meningitis, acute benign encephalomyelitis, Iceland's disease, neuromyasthenia, benign myalgic encephalitis).—These descriptive terms and several others indicate the clinical syndromes of acute aseptic meningitis produced by the poliomyelitis, Coxsackie (19) and ECHO (20) viruses and similar epidemic illnesses in which the etiology is uncertain (21, 22). Enteric bacteria had at least a commensal role in some outbreaks (22). Individual cases probably cannot be

separated clinically from the diseases just described but epidemic occurrence is more likely. Other disorders with a major neurologic component, such as paralytic poliomyelitis, epidemic encephalitis and acute infectious polyneuritis (Guillain-Barré syndrome) will not be discussed.

The syndrome of abortive poliomyelitis is mimicked clinically by a number of other agents. Infection with the Coxsackie and ECHO viruses may account for as much as 40% of aseptic meningitis previously believed to be abortive poliomyelitis. Also, many cases have occurred during epidemics of paralytic poliomyelitis. Among the Coxsackie A viruses only A-9, and perhaps some untyped strains, produce symptomatic infection of the central nervous system. Probably all the Coxsackie B strains produce such infection, but especially B-3 and B-5. The ECHO viruses (20) are not an immunologic family, but nos. 3, 6, 7 and 9 at least have caused outbreaks of epidemic acute benign meningoencephalitis.

The illness may be either biphasic with nonmeningeal, often gastrointestinal, prodromal symptoms or of acute onset, with meningeal symptoms, myalgia or transient neurologic abnormalities. Infants, children and young adults are usually affected. Some of the syndromes are characterized in intense myalgia, dysthesias and muscle tenderness. A macular skin rash may occur with certain Coxsackie and ECHO viruses. Some enlargement of the lymph nodes is common. Weakness, especially of the limbs, flaccid paralysis, usually transient, and sensory deficits are frequent. The degree and persistence of functional muscle impairment vary markedly. Nuchal rigidity is usual, but not always evident. The temperature is variable but often moderate. The course of the disease is brief in most outbreaks, but in others myalgia and weakness have persisted for many weeks.

Subacute and Chronic Meningitis

The onset of symptoms with some types of meningitis is insidious and their progression is irregular, often slow and remitting. The principal differential diagnosis, after the recognition of subacute and chronic meningitis, is among tuberculosis, syphilis and fungal infections.

Subacute meningitis, tuberculous.—The clinical syndrome of tuberculous meningitis is often distinctive (23), but occasionally the onset may be so abrupt and symptoms so

severe that it mimics acute purulent meningitis. More often, the infection must be differentiated from acute aseptic meningitis or chronic meningitis of nontuberculous origin. Although the greatest frequency is in the second year of life, cases occur in all age groups. Radiographic pulmonary lesions are present in more than half of patients.

Onset of symptoms is gradual in about two thirds of childhood cases and in most adult patients. Cerebral symptoms predominate. Drowsiness, listlessness, apathy, loss of interest in regular activities, sometimes irritability, restlessness, confusion or mild delirium may characterize the initial stage of illness. Headache, vomiting and nuchal rigidity are not so prominent as with the acute meningitides. Headache is likely to be remitting. Attacks of vomiting without apparent cause are prone to occur in infants and young children. Symptoms develop over a period of a few days to a few weeks, and brief periods of apparent good health may intervene. As the infection progresses, dullness and apathy deepen into stupor and delirium; generalized and focal convulsions are not unusual.

Temperature is usually elevated only slightly. It may be markedly irregular and even subnormal. Although respirations may appear grossly normal, they become irregular during sleep and stupor. Nuchal rigidity increases as the disease progresses, but board-like rigidity and opisthotonos are not frequent. Neurologic manifestations, especially cranial nerve palsies, are common and of great assistance in differential diagnosis. They occur in at least 40% of patients with tuberculous meningitis. The oculomotor and abducens nerves are especially likely to be affected. Ptosis, pupillary inequality, strabismus, occasionally nystagmus and weakness of the ocular muscles occur. Papilledema is not infrequent late in the course, and miliary tubercles are occasionally seen in the choriod. Vasomotor abnormality of the skin causes marked dermatographia, referred to as *tache cérébrale*. Hypertonus, monoplegia or hemiplegia are characteristic. Deep tendon reflexes are increased and pathologic reflex responses are often elicited.

The tuberculin skin test is positive in all but a few patients. Leukocytosis is not present in early stages but may occur late in the illness even to the extent of a leukemoid reaction.

Observation of the patient for a few days along with examination of CSF frequently permits an unequivocal clinical diagnosis.

SUBACUTE AND CHRONIC MENINGITIS, NONTUBERCULOUS — The clinical syndrome of chronic nonpurulent, nontuberculous meningitis is usually caused by syphilis, fungi or parasites (11, 23, 24, 25). All these infections produce a primary infection other than meningitis, which may go unnoticed or be forgotten. Pulmonary and cutaneous lesions are most common, serving as a portal of entry. Chronic meningitis can occur from complicated or atypical forms of acute and posttraumatic meningitis or infections secondary to meningomyeloceles.

Syphilitic meningitis has a subacute or chronic course (24). Headache, nausea, vomiting and papilledema are major manifestations. Some develop focal neurologic symptoms, such as convulsions, monoplegia, hemiplegia or aphasia, or disorders of cranial nerve function. Almost any cranial nerve may be affected, and the involvement may be unilateral or bilateral. Optic neuritis with visual impairment occurs in some instances. Neck stiffness may be found, but sometimes is absent.

Cryptococcosis (torulosis) of the central nervous system causes a clinical syndrome similar to tuberculous meningitis. Cerebral manifestations are clinically less prominent. Spontaneous remission and relapses are common. The chief complaint of patients is usually chronic headache, diplopia, blurred vision, dizziness or ataxia. Diarrhea is not infrequent in the initial stage of cryptococcosis, and myxomatous skin lesions have been observed. Papilledema and pathologic responses of the deep tendon reflexes are often present. As noted previously, many patients have another underlying disease.

MENINGISMUS

Meningismus is a term that has been used to designate a condition characterized by signs suggesting meningeal inflammation in the absence of true inflammation of the meninges. These signs, such as headache, vomiting and nuchal rigidity, have some cause other than meningeal infection or inflammation, although in some cases an irritation of the meninges can be presumed. Meningismus may occur in some neurologic disorders; it may be on a hysterical or muscular basis, or can be caused by mechanical, toxic or, possibly, allergic factors. The syndrome sometimes develops as part of acute infectious diseases. Also, there are other noninfectious conditions, such as acute renal failure, acute alcoholic delirium, intoxication with one or another of many drugs, and trauma, all of which can

produce the features of meningismus. Fever, localized neurologic signs and pathologic reflex responses are *not* manifestations included in the syndrome of meningismus.

Serous Meningitis (Toxic Meningitis)

Use of the term "meningismus" by some clinicians to describe another syndrome has caused confusion regarding the physiologic and pathologic significance of the diagnosis and its etiologic implications. Although "meningismus" may appear to be a prelude to serous meningitis, it is advisable to distinguish between them. Meningismus implies a normal CSF, without pleocytosis or elevation in pressure. Serous meningitis, on the other hand, is associated with sterile inflammation of the meninges. It can occur among patients with bacillary dysentery in which a neurotoxin is absorbed from the gastrointestinal tract, acute streptococcal infections, especially scarlet fever (26) and other severe infections. A certain proportion of the acute meningoencephalitides from contagious diseases of childhood may also be a toxic meningitis rather than infection per se. In all these examples CSF pressure may be elevated and the cell count normal, or slightly increased.

Acute serous meningitis has been observed after operations performed under spinal anesthesia and following the subarachnoid injection of serum or drugs. Reactions to the parenteral injection of hyperimmune serum also have been reported as a cause of serous meningitis, and the syndrome of postvaccinal and postinfectious serous meningitis appears to be related to the antibody response or hypersensitivity of the host rather than to an invasive infection. In these situations, both the cell count and CSF pressure, as well as protein, may be significantly increased. The term "serous meningitis" also has been used for the syndrome of "pseudotumor cerebri," in which marked elevation in intracranial pressure occurs without pleocytosis. Some of these cases appear to be due to dural sinus thrombosis. This condition should be set apart from the disorders discussed previously.

Meningismus or acute serous meningitis can be suggested clinically, but a lumbar puncture should always, or nearly always, be performed to exclude true meningitis and to assist in the differentiation of other possible conditions.

Parameningeal Infection and Tumors (Sympathetic Meningitis—False Meningitis)

Abscess in the brain, or in the subdural or epidural spaces, secondary to acute sinusitis, otitis media, vertebral osteomyelitis or intervertebral chondritis are infections that may lead to nuchal rigidity and pleocytosis of CSF, without invasion of the meninges by the organism. Severe headache, vertigo, apathy or mental dullness, convulsions, vomiting and even cranial nerve palsies associated with the intracranial abscesses further complicate the picture, but these manifestations are due to the abscess masses themselves. Initially, they are all localized infections, and this fact can be differentiated by a careful history and examination of the patient. Proximity of the infection to the meninges may cause a mild "sympathetic meningitis," because of local involvement of the leptomeninges by the inflammatory process without extension of organisms through this barrier. All these lesions can, of course, produce a secondary acute purulent meningitis.

Tumors, either primary or metastatic in origin, may be situated near the meninges (27). Headache, vomiting, changes in personality and state of consciousness, convulsions and various neurologic manifestations may lead to a suspicion of meningitis, although these features are due to parenchymal involvement. The CSF findings could even further the suspicion, as pleocytosis from necrosis in the tumor, along with elevated protein and pressure, can occur.

A rare disorder is the spread of primary or metastatic brain tumor throughout the meninges. A gliomatosis, carcinomatosis or sarcomatosis of the meninges results. Cranial nerve or spinal root involvement may lead to pain and neurologic deficits. The picture is that of a chronic meningitis, except for the prominence of root pain. The CSF findings confirm the diagnosis of meningitis, for elevation in cells, protein and pressure occur and, rarely, even the sugar is reduced. Findings of tumor cells in the CSF may establish the diagnosis. These situations are rare, and an accurate clinical appraisal of the situation usually can be made.

CLINICAL-PATHOLOGIC CORRELATION

Although antibiotic therapy has greatly reduced the morbidity from meningitis, disabling complications and fatalities

still occur. It is pertinent, therefore, to record the pathology of meningitis (14, 28, 29, 30), along with a review of clinical manifestations, to obtain a thorough understanding of the disease. Also, examination of CSF, valuable as it is in the diagnosis and for following the course of meningitis, does not fully reflect many changes that can occur in the nervous system, if the course becomes complicated. The clinician must therefore know what possibilities to expect as the disease unfolds.

Acute Purulent Meningitis

The most comprehensive analysis of sequential pathologic changes and their clinical counterpart in meningitis has been described by Adams, Kubik and Bonner (14) for *H. influenzae* meningitis. The phenomena described for this organism are similar, with minor variations, to those for all pyogenic organisms causing acute, purulent meningitis. For convenience, evolution of the events in acute purulent forms can be subdivided into 4 successive phases: early, acute, subacute and late.

The early phase.—The early phase covers the 24-48 hours during which the first involvement of the nervous system proper occurs. It is not strictly a stage of the meningeal infection. The features are prominent only in severe, fulminating cases, most characteristically, the meningococcal and pneumococcal infections. Pathologically, one encounters a marked cerebral edema. This appears to be related to the septicemia rather than to invasion of the meninges, for in some cases one can find no cells in the CSF, nor can one culture the organism. The mechanism of the edema is poorly understood; one assumes possible toxic injury to the capillary endothelium.

Whatever the mechanism, the clinical counterpart is dramatic. Fever and toxicity secondary to blood-stream invasion are soon followed by projectile vomiting, stupor, convulsions and, eventually, coma. Headache may or may not be a complaint. Death commonly follows within 48 hours after onset. It is due to the effects of cerebral edema (brain stem compression from herniation of the uncus over the tentorial rim or cerebellar tonsils through foramen magnum) or to the septicemia, or to a combination of these factors.

Therapeutic efforts at reversing the cerebral edema have been discouraging. No effective way is available at present,

although decompression by means of an extensive bilateral craniectomy has been suggested. The clinician needs to keep in mind this occurrence of cerebral edema, while directing therapy toward the specific organism and problems of supportive treatment. In this critical period it is possible to inflict harm by injudicious use of the lumbar puncture. In order to avoid aggravating the herniation brought about by edema, it is advisable not to attempt a lumbar puncture at all during this period in fulminating cases, unless further information is absolutely necessary for a diagnosis.

If a diagnostic lumbar puncture is performed at this time, it is dangerous to remove more than the minimal amount of fluid necessary for a sugar determination, culture and cell count. It is especially unwise to attempt to lower CSF pressure, as is done therapeutically once full-blown meningitis has developed and the elevated pressure can be related more to the increased volume of CSF than to cerebral edema.

THE ACUTE PHASE.—This phase covers the first 10-14 days after the organisms have gained access to the meninges and are actively proliferating, regardless of whether the route of entry was the blood stream or extension from an adjacent focus of infection.

The initial response of the pia-arachnoid is one of intense vascular congestion (Fig. 1). This is soon followed by an exudative reaction composed predominantly of neutrophils and fluid of high protein content, including fibrinogen. Although moderate edema may be present, one usually encounters minimal or only slight brain swelling. Grossly, the meninges initially exhibit a slight cloudiness, but as the exudative response becomes more marked there develops a thick, fibrinous, grayish or greenish exudate in the subarachnoid space. This may surround the spinal cord, but over the brain it tends to be concentrated in the cisterns, along the ventral surface of the brain stem, in the sylvian fissures and in the cortical sulci over the convexity of the cerebral hemispheres. In severe cases the exudate covers the entire surface of the brain, as shown in Figure 2.

During these first several days the classic symptoms and signs of meningeal inflammation are seen. Neurologic disturbances also may be marked. Early severe neurologic manifestations exist in the striking absence of significant microscopic changes in the nerve cells of the brain. Perivascular infiltrates in the subpial tissue constitute the only noteworthy

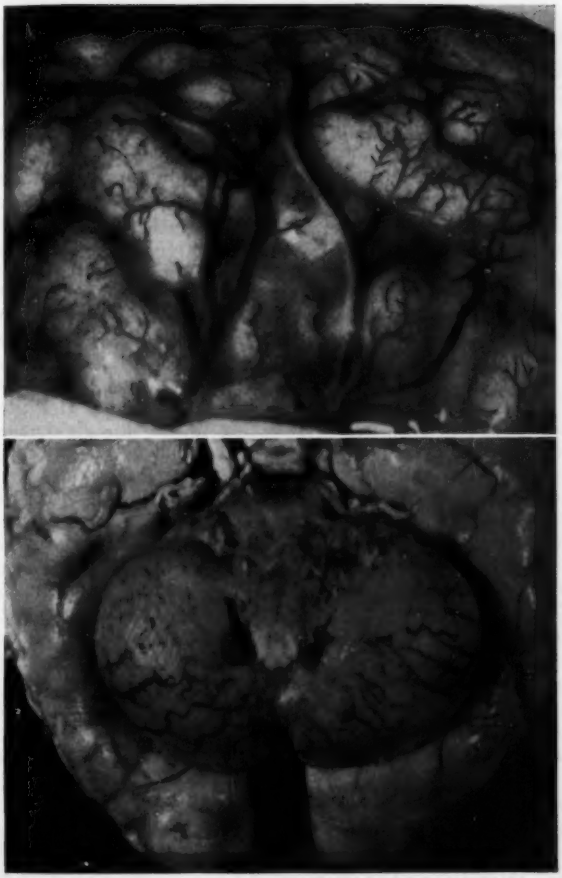

FIG. 1 (*top*).—Pneumococcal meningitis, showing early meningeal reaction with vascular congestion and suppuration along veins. (From Robbins, S. L.: *Textbook of Pathology* [Philadelphia: W. B. Saunders Company, 1957].)

FIG. 2 (*bottom*).—Thick, creamy exudate over entire surface of cerebral cortex, brain stem and cerebellum that may develop in overwhelming purulent meningitis.

parenchymal change. This discrepancy between the clinical state and microscopic findings in the brain substance can only be attributed to the inadequacy of our histologic technics.

Concomitant with these pathologic and clinical events, CSF pressure is elevated, in large part due to increase in volume of the fluid from capillary transudation. If present, cerebral edema contributes to this. The cellular response is predominantly neutrophilic. The cellular and biochemical changes in the CSF will be presented later.

After the first several days of illness, particularly during the second week, cases refractory to therapy display advancing pathologic changes at the microscopic level. The neutrophilic response is gradually replaced by a mononuclear reaction, consisting mostly of lymphocytes and histiocytes. These collect over the pia, with the degenerating neutrophils lying more peripherally. Cranial and spinal nerve sheaths contain cellular infiltrates, and similar extension is noted in the adventitia of meningeal arteries and veins. Definite alterations are evident in the cortex, as manifested by degeneration and even loss of nerve cells. Microglial phagocytes appear, and astrocytes swell and multiply in response to the injury. There is a minimal neutrophilic infiltration. This acute cortical degeneration is not considered a true encephalitis or cerebritis due to bacterial invasion. Toxic and ischemic factors have been implicated, but this is an aspect of meningitis not well understood.

During the downhill course in the second week, the patient is in semicoma or coma, and nearly always is a problem in seizure control. The convulsions may be focal or generalized. In most cases they are secondary to acute cortical damage. Cranial nerve palsies also appear and indicate that serious injury to nerve fibers may accompany the extension of the inflammatory process to the nerve sheaths. Fatality during the acute phase of meningitis is usually attributed to the severe meningeal infection, with its attendant severe disturbances in brain function.

THE SUBACUTE PHASE.—If a patient survives the first 2 weeks of illness, but continues to have an uncontrolled meningitis, there is relentless progression of complicating pathologic processes which began to appear in the previous phase. New developments also are added.

The continued exudative process is characterized by an increasing predominance of mononuclear cells over neutrophils.

The latter degenerate and undergo phagocytosis. Fibroblasts and capillaries proliferate, in an attempt to organize the purulent material, so that the exudate becomes more dense and cohesive on gross examination.

Adventitial inflammation of meningeal arteries and veins becomes marked, accompanied in some by necrosis and inflammation of the media. Subendothelial accumulations of inflammatory cells can be found in scattered arteries. Necrosis of the vessel well may lead to thrombosis of veins, although this rarely occurs in arteries. Thrombophlebitis of veins overlying the cortex may lead to small foci of venous infarction, which can cause convulsions and, less frequently, focal neurologic signs. Rarely is dural sinus thrombosis a complication.

Progression of cortical degeneration sometimes results in frank necrosis. Nerve-cell loss is widespread, and reactive microglial phagocytes and astrocytic hyperplasia become marked. When cortical involvement is this severe, seizures, reflex changes, spasticity and even hemiparesis may be found.

Organisms gaining access to the ventricles may set up foci of subependymal inflammation, with focal destruction of the ependyma, and perivascular cuffing of inflammatory cells. Rarely a diffuse ventriculitis results.

Another infrequent, but serious, complication is subdural empyema which intensifies the thrombophlebitis and underlying cortical necrosis. The appearance of progressive focal signs should alert the clinician to the possibility of subdural pus. Since these clinical features may also be due to cortical degeneration or thrombophlebitis from the meningitis alone, subdural empyema can be excluded only by trephine examination. In the face of progressive focal signs and a steadily downhill course then, burr-hole inspection of the subdural space is the only way of making a diagnosis. Surgical intervention in this instance may be lifesaving.

A more common type of subdural involvement is effusion into the subdural space. Almost exclusively a complication of meningitis in infancy, its greatest incidence is in *H. influenzae* meningitis, although it may occur in any purulent meningitis (31, 32). The mechanism of this effusion is not known. It may simply be comparable to pleural effusion with pneumonia. Its occurrence is not entirely confined to this phase of meningitis, as it sometimes occurs during the first week or two of illness.

The fluid collects in the subdural space over the cerebral

cortex, and around it there gradually forms a connective tissue membrane arising from the dura. The contents are usually sterile. There is a high protein content, and the fluid is slightly yellow colored or, rarely, colorless. Although grossly clear, mononuclear cells are found on stained smears. This subdural pocket of fluid may gradually enlarge and produce serious neurologic derangement. Persistent or deepening stupor, convulsions or hemiparesis, along with enlarging head size, constitute the clinical spectrum. Surgical drainage is imperative, either by subdural taps or through trephines. It appears doubtful that removal of the membranes is necessary, although some recommend this.

THE LATE PHASE.—Cases in this phase include patients who survive a month with protracted activity of the meningeal infection and those in whom the infection was finally controlled during the subacute phase. The chief characteristics of this phase relate more to the progression of the reactive processes than to damage from the infectious agent per se.

The major pathologic change is the development of hydrocephalus. This may become severe and lead to marked ventricular enlargement (Fig. 3). Organization of exudate ultimately leads to a fibrous matting of the inflammatory material and vessels. This is most striking around the brain stem. Location of this in the region of the foramina of Magendie and Luschka, with blockage of the exit of CSF from the 4th ventricle, is an important factor in the pathogenesis of hydrocephalus. Probably an equally important one is the obliteration of the subarachnoid space around the brain stem by the meningeal fibrosis, preventing the flow of CSF upward through the subarachnoid space to the arachnoid villi which drain into the sagittal sinus.

A final cause of hydrocephalus is obstruction of the aqueduct of Sylvius. Foci of ependymal destruction and subependymal inflammation, usually beginning in the subacute phase, eventually lead to glial scarring and small granulations which protrude from the surface of the ependyma. In the aqueduct, these may lead to critical reduction of the lumen and prevent ready flow of CSF from the 3rd into the 4th ventricle.

Clinically, head enlargement is obvious in infants. In children, the sutures may separate. Persistent headache and vomiting from increased pressure may occur in both children and adults. Eventually, progressive mental obtunding, spasticity with increased deep tendon reflexes in the legs, even

paraparesis, develop as the condition advances. It is ultimately fatal.

Progressive hydrocephalus does not always occur, but these patients have not escaped widespread cortical necrosis and foci of infarction secondary to thrombophlebitis. Dementia, often severe, along with focal or generalized convul-

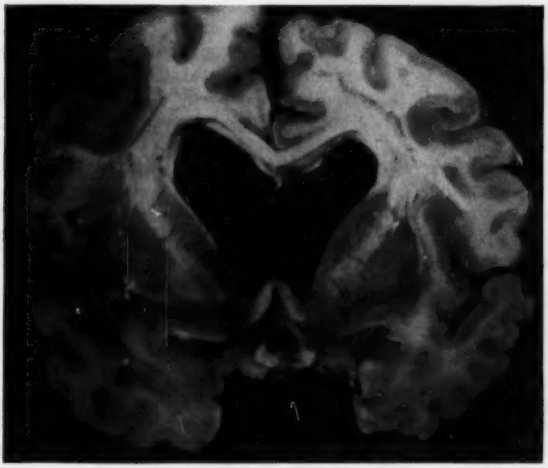

FIG. 3.—Obstructive hydrocephalus in late phase of purulent meningitis. Septum pellucidum is attenuated and ventricles moderately dilated.

sions, and focal neurologic deficits in both motor and sensory spheres are clinical phenomena seen in this phase.

Little has been said about the spinal meninges and cord. They share in the inflammatory process, as it evolves over the brain. In severe cases a block develops in the spinal subarachnoid space. Little parenchymal damage occurs, however, until the late phase. As a result of progressive fibrosis, vascular supply to the periphery of the cord through small pial vessels may become compromised. This may lead to impairment of position and vibration sense resulting from posterior-column involvement, and spastic weakness with in-

creased deep tendon reflex activity in the legs, from lateral-column damage.

Acute Aseptic Meningitis

The pathologic picture in acute aseptic meningitis is a diffuse inflammation of the leptomeninges. The exudate is almost entirely composed of lymphocytes and the inflammatory response is less than in most cases of purulent meningitis. There is not more than a small percentage of neutrophils, and little fibrin is poured out in the exudate.

Beyond a lymphocytic cuffing of vessels in the meninges and outer layers of the cortex, none of the pathologic complications described in purulent meningitis develop. Conspicuously absent are the infiltration of vessel walls, thrombosis, degeneration or frank necrosis of the cortex, and the organization and fibrosis of the meningeal exudate leading to hydrocephalus. Limited to the meninges, the course is nearly always benign. Headache, vomiting and nuchal rigidity occur as a result of the meningeal inflammation and elevated intracranial pressure. When the process subsides, the meningeal exudate is removed, and no residual pathologic or clinical abnormality is subsequently demonstrable.

If neurologic signs appear during the course of illness, this indicates an extension of the infection into the parenchyma of the brain or spinal cord. In viral infections, this implies invasion of neurons, with ultimate necrosis and death of many of those infected. When this develops, clinical features are those of an encephalitis or myelitis, and no longer an aseptic meningitis in the strict sense.

Subacute and Chronic Meningitis

Tuberculous.—Basic aspects of the pathologic process observed in acute purulent meningitis are observed also in tuberculous meningitis. The tempo of the two diseases differs, so that the pathologic and clinical picture in a typical case of tuberculous meningitis resembles that in the subacute and late phases of purulent meningitis.

The inflammatory response is low grade, with the characteristic changes of tuberculosis, namely, collections of lymphocytes and epithelioid cells. Langhans' giant cells and foci of caseation necrosis may not be prominent. Neutrophils par-

ticipate in the early response. The process is most intense at the base of the forebrain, over the brain stem and over the inferior surface of the cerebellum. There is some inflammatory necrosis of the wall and, ultimately, thrombosis of both arteries and veins. In contrast to purulent meningitides, arterial thrombosis is a frequent complication, often resulting in ischemic infarction.

Because tuberculous infections stimulate a vigorous, proliferative response, a marked fibroblastic reaction appears early. This continues throughout the course, the exudate gradually becoming enclosed in a dense meshwork of fibrous tissue. The outcome of the meningitic process is the production of a thick, matted, partly gelatinous, often slightly greenish exudate primarily located over the base of the brain. In addition, spread of organisms within the ventricles often leads to focal ependymitis, with subsequent formation of ependymal granulations.

The manner in which the various component pathologic processes contribute to the clinical manifestations is comparable to that from similar changes in purulent meningitis. The lesser intensity of the meningeal inflammation in tuberculous meningitis results in less severe clinical signs of meningeal inflammation. Some of the early cerebral symptoms, such as drowsiness and apathy, are undoubtedly related in part to the concomitant increase in intracranial pressure.

Thrombosis of arteries of varying sizes leads to cerebral and brain-stem infarcts and symptoms related to ischemic necrosis. These account for many of the focal phenomena, such as monoplegias, hemiplegias and convulsions. Tuberculomas within the brain also account for focal manifestations in some cases. As cranial nerves become surrounded and compressed by the exudate and fibrous tissue, cranial nerve palsies appear. Finally the fibrous obliteration of the subarachnoid space around the brain stem, occlusion of the foramina of Magendie and Luschka, and, in a few cases, aqueduct narrowing by ependymal granulations, combine to bring about a progressive hydrocephalus. Exudative, scarring, vascular and pressure factors probably all enter into the final interference with brain-stem function which leads to deepening coma and death.

NONTUBERCULOUS.—Meningitides in this group share the pathologic features of subacute and chronic meningitis in general. The inflammatory response is more intense in some

cases, of lower-grade intensity and extremely chronic in others. It is always primarily a mononuclear response. Lymphocytes, histiocytes and, especially in syphilitic meningitis, plasma cells participate. The process is usually most fully developed over the base, although the involvement is occasionally greater over the cerebral hemispheres. Productive fibrosis ultimately ensues in response to the exudate.

For a considerable time, meningeal symptoms comprise the clinical picture. Eventually, as cranial nerves become surrounded by exudate and scar tissue, cranial nerve deficits appear. In syphilitic as in tuberculous meningitis, focal neurologic signs and symptoms indicate the development of arteritis, with thrombosis and infarction. In cryptococcal meningitis, arteritis may occur, but focal manifestations usually indicate extension of the organism into underlying brain tissue via the Virchow-Robin spaces, with ultimate formation of small cysts containing organisms.

In all members of this group, meningeal fibrosis obliterating the subarachnoid space around the brain stem and obstructing the 4th ventricle outlets leads to hydrocephalus, causing persistent headache, vomiting and papilledema. Ependymitis may be followed by granulations which contribute to this, but it is not common.

Meningismus and Serous Meningitis

It is least confusing to confine the term "meningismus" to those situations in which signs of meningeal inflammation are detected clinically but in which lumbar puncture fails to disclose any abnormality (p. 19). Although "serous meningitis" implies abnormal CSF findings, there is no clearly defined pathology. A diffuse, mononuclear type of inflammatory response is presumed. In some, where pressure is elevated and CSF clear, there is no structural abnormality. The clinical picture in these cases is apparently related entirely to the increased intracranial pressure.

Parameningeal Infection and Tumors

Inflammation of the meninges in response to an adjacent focus of infection or tumor growth is localized. It is an incidental phenomenon, with minimal or no clinical meningeal signs and symptoms, unless the infection or neoplasm becomes disseminated throughout the meninges.

PROGNOSIS

Many factors enter into the prognosis of patients with meningitis. In all forms, age influences survival rates, death occurring more often in infants.

Extremely high CSF pressure early in acute, purulent meningitis is an untoward sign. Some mortality statistics are given in Treatment and Prevention (p. 50). Patients who recover from acute, purulent meningitis, and have had none of the complications which may accompany the inflammation, can expect to be free from residual clinical or pathologic sequelae. The inflammatory exudate is removed without organization and subsequent fibrosis, and there is no indication of residual brain damage.

The late prognosis in cases of severe purulent meningitis, and in all forms of subacute and chronic meningitis, is determined primarily by the complicating involvement of structures other than the meninges, and by the proliferative fibrotic reaction rather than by the meningeal infection per se. Cranial nerve palsies generally improve, if there is recovery from meningitis, although deafness persists in a high proportion of patients in whom it develops. Focal neurologic deficits as a result of infarct necrosis subsequent to arteritis or phlebitis tend to improve as the patient recovers. The degree of improvement depends largely on the size and location of the lesion. Persistent convulsions throughout the illness usually indicate underlying structural cortical damage. Such areas often persist as epileptogenic foci after recovery and sometimes create difficult problems in seizure control.

Patients who have extensive destruction of cortex in purulent meningitis, or in tuberculous meningitis, or who have numerous cortical cysts in cryptococcus meningitis, characteristically will be markedly confused, inattentive and retarded in mental function as they recover. Subsequently, the more severe cases display a distressing loss of intellect, and become lost to society as useful people, despite recovery from meningitis.

Persistent, increased intracranial pressure during recovery usually is secondary to fibrotic obliteration of the subarachnoid space around the brain stem, or the 4th ventricle outlets. This hydrocephalus may unfortunately be progressive, even though the meningitis has subsided. Ultimately, optic atrophy, blindness, weakness and spasticity, especially of the legs, and mental deterioration are consequences, with eventual fatal

termination. Neurosurgical by-passing procedures, if successful, may prevent this course of events.

Symptoms related to the posterior and lateral columns of spinal cord and to spinal roots rarely develop from severe fibrosis of spinal meninges.

Acute aseptic meningitis and serous meningitis are usually not followed by any sequelae. Exceptions would be the complicating development of encephalitis or myelitis in the case of virus infections, and the rare case of adhesive arachnoiditis that might occur in certain forms of serous meningitis, such as that following intrathecal anesthetics.

NEUROLOGIC EXAMINATION

The most decisive clinical information regarding the presence or absence of meningitis is obtained from signs directly related to inflammation of the meninges. The meningeal sheaths of the posterior spinal roots share in the generalized process in the meninges, and when these inflamed sheaths are put on a stretch by any maneuver, impulses are set up in underlying pain fibers. Such maneuvers are uncomfortable and initiate a local reflex that maintains a strong spasm of the muscles which hold the craniospinal axis rigid. This apparently protective mechanism underlies the signs related to meningeal inflammation (23, 29).

Meningeal Signs

Meningeal signs are the earliest to appear, apart from those of systemic infection, and therefore it is important to recognize slight degrees of them. Although they are not absolutely specific for meningitis, they are fairly constant in its various forms.

1. *Posture.* The patient lies somewhat rigidly. Movements are avoided. If asked to sit, he finds it painful to assume a full sitting position. The head and spine are held rigidly, with knees flexed (Fig. 4).

In severe cases, particularly in infants, a posture of extreme extension of the neck with extended thighs and flexed knees (opisthotonos) is observed.

2. *Kernig's sign.* With the patient supine and the thigh

flexed over the abdomen, one finds pain and limitation of motion, with attempts to straighten the leg at the knee (Fig. 5). Normally it should be possible to carry this to an angle of approximately 135 degrees between the lower leg and thigh. In

FIG. 4.—Rigid posture of head and neck in sitting position in patient with early meningitis. Knees may be flexed.

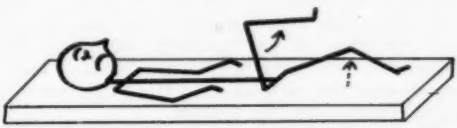

FIG. 5.—Painful limitation of straightening leg at the knee, with thigh initially flexed over abdomen (Kernig's sign). The opposite leg may be flexed simultaneously (dotted arrow).

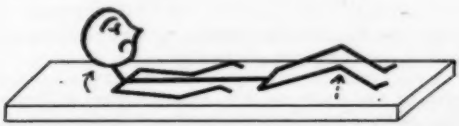

FIG. 6.—Limitation of neck motion, often painful, with elevation of head in supine position. Sometimes the knees are reflexly bent (Brudzinski's sign).

attempting to relieve the discomfort, the patient will simultaneously flex the opposite leg slightly, as in Figure 5.

3. *Neck movement.* Asking the patient to touch his chin to his chest, or passive motion of the head in the supine position, discloses painful limitation of neck movement (Fig. 6).

4. *Brudzinski's sign.* While testing freedom of neck motion, the patient may be observed to flex both legs slightly as the head is brought forward (Fig. 6). This is a compensatory movement which diminishes the discomfort.

5. *Pronounced irritability.* This is less specific evidence of meningeal inflammation, but at least in part related to it. Also, one may observe hypersensitivity to skin stimuli, so that clothes, bed sheets or anything touching the skin surface is annoying.

Beyond the signs of meningeal inflammation, a careful neurologic examination will disclose additional features, depending on the stage of infection and extent of parenchymal nervous-tissue involvement.

Mental Status

Examination discloses varying degrees of mental abnormality. Whether the general picture is one of delirium or drowsiness, confusion and disorientation are usually part of the mental disturbance. In the early phase of meningitis, slight degrees of confusion and disorientation may be most helpful in alerting the physician to the presence of a disease involving the central nervous system.

Cranial Nerves

Impairment of cranial nerve function may occur in severe purulent meningitis, but usually not until the end of the first week. In the chronic basilar forms, such as tuberculous meningitis, it may appear as an early sign.

Nasal congestion of the optic disks may accompany cerebral edema in the early stages. Papilledema is found later in association with complicating hydrocephalus. Optic atrophy and impaired vision may follow in such cases or may result from inflammation and secondary damage to the optic nerve itself.

Pupillary inequality, with either miosis or mydriasis, and sometimes fixed pupils, which are particularly sensitive signs in meningitis, should be looked for carefully. Extraocular palsies are less common except in tuberculous or other forms of chronic meningitis. Sixth-nerve palsy with weakness on lateral gaze is the most frequent. Rarely is the 5th nerve se-

verely involved. Seventh-nerve involvement is of a lower motor neuron type, with equal degrees of weakness in the upper and lower face. This is usually only partial in degree. Hearing loss and vestibular disturbances are manifested in severe purulent meningitis and in chronic basilar meningitis. The other cranial nerves are seldom affected to a clinically significant degree.

Motor System

Examination infrequently discloses any striking abnormality in early meningitis, with the exception of convulsions and rigidity of spinal muscles. The former may be focal or generalized, or consist of generalized myoclonic jerks.

If severe cortical injury develops, hemiparesis or monoparesis may appear, accompanied by spasticity or rigidity. A degree of alteration in muscle tone on passive motion may be present without gross weakness. Deep tendon reflexes are normal in the early phases and become hyperactive when other signs of cortical damage appear. A Babinski sign is often present early or late in the disease, with or without other motor signs.

It is well to observe carefully the character of the respirations. Biot's respiration is an irregularity in the rate and amplitude of breathing. It is an indication of critical disturbance of brain function in seriously ill cases.

Sensory Examination

Sensation is rarely disturbed beyond the hypersensitivity to cutaneous stimuli related to inflammation of the meninges around the spinal roots.

A final word should be devoted to observation of head size. In either acute or chronic meningitis in infants, increasing head size is a manifestation of a serious compromise in the flow of CSF, with resultant hydrocephalus.

EXAMINATION OF CEREBROSPINAL FLUID

Although meningitis is properly viewed as a disease state of the meninges and not of the CSF, the latter has a basic role in the disease (33, 34). It serves as a culture medium for the growth of organisms once they reach the meninges and

certainly serves to spread them as well. It accommodates the exudate poured out in the inflammatory response to the infection, and reflects the struggle between the organisms and the body's defenses. Furthermore, disturbances in circulation of CSF are an integral part of meningitis, with important clinical and pathologic consequences.

The diagnosis of meningitis is customarily considered to be established only after obtaining evidence of meningeal inflammation from CSF findings, and it is understandably essential to have a sample of CSF to make an accurate etiologic diagnosis. Beyond this, examining the CSF is of substantial aid in following the patient's response to therapy and in evaluating the nature and extent of the underlying pathology, if complications develop.

It is important to recognize, however, that CSF does not yield sufficient data to reveal the total picture of the meningeal process. A careful appraisal of the clinical state, as well as of CSF, is necessary at all stages to be able to make a thorough analysis of the patient's status. Only by such complete analysis can the first clues be detected, pointing to a resolution of the process on the one hand, or disturbing complications related to an intractable course on the other.

Examination of CSF should be performed as soon as possible after collecting the fluid and should include the following studies.

Pressure

Both opening and closing pressure of CSF should be noted. One expects slight to marked elevation in bacterial meningitis. In nonbacterial meningitis, pressure is more often normal, but it may be increased. In certain situations the danger from lowering pressure, when elevated, is discussed under Clinical-Pathologic Correlation (p. 20). In acute, fulminating cases associated with septicemia, pressure elevation is a result of cerebral edema to a large degree, and one should remove only the minimal amount of fluid necessary for diagnostic studies. Once an extensive meningeal exudate has developed, hypervolemia of CSF is a major factor in the rise of intracranial pressure, and lowering the pressure for symptomatic relief as well as laboratory studies seems justified.

Under no circumstances should a Queckenstedt test be carried out, unless there is positive clinical evidence suggest-

ing a spinal block, which is rare in meningitis except as a late complication.

Appearance of the Fluid

A turbid fluid generally means a cell count of at least 150-200 per mm^3. There may be a slight opalescence. Sometimes a yellowish or greenish hue is noted, the latter suggesting in particular a pneumococcal infection. A faint yellow usually indicates a high protein (over 150 mg.%). On standing a few hours, protein precipitation may lead to the appearance of a web-like clot, which is coarse in purulent meningitis, and fine in the more chronic forms.

Cell Count

The enumeration of cells is performed in a hemocytometer. A dilute stain, such as 0.4% methylene blue, will aid in the differentiation of red and white blood cells. The stain is drawn into a white-cell pipette up to the 1 mark, and then CSF to the 11 mark. After shaking and introducing a drop of the fluid into the chamber, a count is made, and the result converted to the number of cells per mm^3. Further details are available in standard texts (33, 35).

Normally, there should be no more than 5 cells per mm^3. If the count is increased, some of the fluid should be centrifuged, and a film from the sediment prepared on an albumin-coated slide, stained with Wright's stain, and a differential cell count made. This should be accurate, for whether the cellular reaction is predominantly neutrophilic or mononuclear is of considerable diagnostic importance.

The cellular characteristics in the various meningitides are summarized in Table 1. A few general guides, however, are useful to remember. A predominantly neutrophilic cell count in the thousands bespeaks an acute, purulent meningitis. Although the cell differential subsequently becomes chiefly mononuclear, some neutrophils almost invariably persist, if the course becomes prolonged. In the subacute and chronic forms of meningitis, whether tuberculous or nontuberculous, a predominant mononuclear response is expected. Some neutrophils are usually found initially in tuberculous meningitis, occasionally 50% or more of total cells. Eventually the cells are almost exclusively mononuclear.

TABLE 1.—RANGE OF CEREBROSPINAL FLUID FINDINGS IN VARIOUS FORMS OF MENINGITIS

	PRESSURE MM. H_2O	APPEARANCE	CELLS PER MM^3.	CELL TYPE	PROTEIN MG./100 ML.	GLUCOSE MG./100 ML.	SPECIAL FEATURES
Normal	80–180	Clear, colorless	0–5	Exclusively mononuclear	15–45	50–80	
Acute purulent meningitis Early phase	Normal to 600	Turbid, opalescent, may be purulent; at times faintly yellow or green; coarse clot	300–20,000	Mostly PMN	50–1,500	0–45	Organisms usually found in stained smears of sediment
Subacute and chronic phases	Normal to 500; occas. higher	Clear or slightly turbid; opalescent; occas. yellow	25–500	Mostly mononuclear; some PMN persist	50–700	20–45	Chloride often low
Acute aseptic meningitis	Normal to 400	Clear or slightly turbid; at times faintly yellow	10–1,000	Mostly mononuclear	Normal to 150	Normal; rarely reduced	Chloride usually normal. More than a few PMN indicate encephalitis or myelitis
Tuberculous meningitis	Normal to 500; occas. higher	Clear or slightly turbid; opalescent; at times faintly yellow; fine clot	25–1,000	Mostly mononuclear; occas. many PMN early	Normal to 1,500	0–45	Organisms may be found in stained smears of sediment or clot. Chloride usually low
Syphilitic meningitis	Normal to 500; occas. higher	Clear or slightly turbid; may be faintly yellow	25–1,000	Mononuclear	Normal to 300	Normal; rarely reduced	Wassermann positive in nearly all cases. Chloride usually normal.

(Continued)

TABLE 1.—RANGE OF CEREBROSPINAL FLUID FINDINGS IN VARIOUS FORMS OF MENINGITIS (Cont.)

(*Continued*)

TABLE 1.—RANGE OF CEREBROSPINAL FLUID FINDINGS IN VARIOUS FORMS OF MENINGITIS (*Cont.*)

	PRESSURE MM. H_2O	APPEARANCE	CELLS PER MM^3.	CELL TYPE	PROTEIN MG./100 ML.	GLUCOSE MG./100 ML.	SPECIAL FEATURES
							First or mid-zone colloidal gold curve, rarely end zone or normal
Cryptococcal and other fungal meningitides	Normal to 500	Clear or slightly turbid; occas. faintly yellow	25–1,000; occas. higher	Mostly mononuclear	50–200	Normal or reduced	Sugar often low in cryptococcal meningitis
Meningismus	Normal	Clear, colorless	Normal	Normal	Normal	Normal	
Serous meningitis	Normal to 400	Clear, colorless	Normal to 100; occas. higher	Mononuclear	Normal to 100	Normal	
Parameningeal infections and tumors	Normal to 500	Clear or slightly turbid; occas. faintly yellow	Normal to 200	Mostly mononuclear*	Normal to 200	Normal	Disseminated tumors can reduce sugar.

*10–50% PMN usual with parameningeal infections.

The aseptic meningitides show an almost completely mononuclear reaction from the onset. Neutrophils may be present in some viral infections, if there is accompanying encephalitis or myelitis, as in poliomyelitis, equine encephalitis and herpes simplex encephalitis.

Protein

The protein content of CSF is elevated in all forms of meningitis. There are 2 major factors influencing the degree of elevation. One is the intensity of the inflammatory process; the other is interference in the flow of CSF in the subarachnoid space. A heavy exudate may interfere with flow of CSF in the early stages of some forms of meningitis, but the most severe degrees of block occur when organization of the exudate has led to meningeal fibrosis, particularly at the base of the brain.

Additional tests for globulin are only occasionally useful in meningitis. A normal, or mid-zone, colloidal gold curve is found in most forms of meningitis. Syphilitic meningitis may cause a first-zone curve, which could aid in differentiating syphilitic meningitis from other subacute or chronic forms.

Sugar

Along with cell count and bacteriologic investigation, glucose determination is of first-rank diagnostic importance. Reduced sugar levels are characteristic of meningeal infections with pyogenic or tuberculous organisms, and may occur in fungus meningitis. Occasionally, syphilitic meningitis is associated with lowered sugar levels, but this is unusual. Viral and leptospiral infections rarely cause a significantly lowered CSF sugar content (36).

Chloride

In acute, purulent and tuberculous meningitis, CSF chloride is usually reduced. Its level primarily reflects the level in the serum, even though there is evidence for a homeostatic maintenance of electrolytes in the CSF. A low chloride value is not expected in viral fungal and syphilitic meningitis, and such a finding may be helpful in the differentiation between these and tuberculous meningitis.

Bacteriologic and Serologic Tests

Procedures for the bacteriologic investigation of CSF are given in Etiologic Diagnosis (p. 42). The clinician should make certain that appropriate tests are carried out on the pretreatment fluid. Whatever the suspicion as to the etiologic agent, if the diagnosis of meningitis is questioned, a Gram

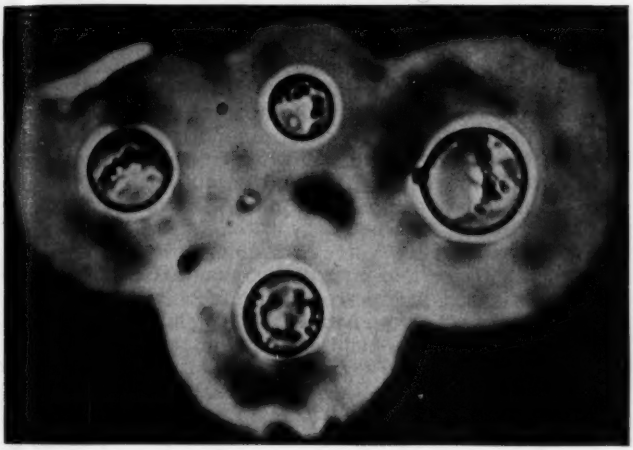

Fig. 7.—Cryptococcus organisms in India ink preparation of CSF. The ink outlines the thick, pale capsule of the organism. (From the Pfizer *Spectrum*, April 21, 1956.)

stain of sediment from CSF should be made. Bacterial infections sometimes are masked as atypical forms of meningitis without the usual CSF findings. If tuberculous meningitis is considered, the sediment and pellicle should be stained for acid-fast organisms. An India ink preparation is particularly useful for *Cryptococcus neoformans*. A drop of CSF is mixed on a slide with a small drop of India ink, and the specimen covered with a coverslip. Under the microscope the capsule of the Cryptococcus organism, brought into sharp contrast from the India ink, has the appearance of a halo (Fig. 7).

A serologic test for syphilis should be performed on all spinal fluids. It will be positive in a high percentage of cases

with syphilitic meningitis. A positive Wassermann test sometimes may be found in nonsyphilitic meningitis when there is systemic syphilis. In a case of meningitis, however, it is strong evidence of syphilitic meningitis. A treponema immobilization test (TPI) should be done if there is a question of a biologic false positive reaction. A quantitative Kahn test is sometimes helpful in evaluating the stage and activity of the disease.

ETIOLOGIC DIAGNOSIS

A definitive diagnosis of the specific microbiologic etiology of meningitis nearly always requires the use of laboratory facilities. It is the physician who must recognize the importance and direct the collection of appropriate specimens for study in the laboratory as soon as meningitis is discovered and before treatment is begun. Both specific treatment of the patient and prognosis are often intimately related to laboratory identification of the etiology of the infection.

Procedures of value vary from simple, readily available tests, such as gross and microscopic examination of CSF, to highly specialized technics, such as inoculation of special cell lines in tissue culture. Nearly all good clinical laboratories have the personnel and facilities to permit study and identification of the common bacterial and fungal causes of meningitis. Only a few laboratories can provide the personnel and facilities necessary to make a complete study and identification of all possible viral and unusual bacterial causes of meningitis. Nevertheless, excellent specialized laboratories are at the disposal of all physicians through local and national diagnostic laboratories of the U. S. Public Health Service. The usefulness of these laboratories, however, depends on the physician's knowledge of proper specimens for study.

Basic methods by which a definite etiologic diagnosis can be made are: (1) Morphologic identification of the microorganism in a stained smear, (2) isolation of the agent by inoculation of selective media, tissue culture, embryonated eggs or experimental animals, (3) serologic demonstration of a specific antigen in acute-phase specimens or, more often, type-specific antibody in the convalescent-phase serum or CSF with a significant increase above the initial specimen and (4) biopsy specimens or skin tests which occasionally permit a positive diagnosis. The application of these methods in various kinds of meningitis is given in Tables 2, 3 and 4.

TABLE 2.—ETIOLOGIC DIAGNOSIS OF BACTERIAL MENINGITIS

BACTERIAL ETIOLOGY	CSF SMEAR		ISOLATION OF AGENT					SEROLOGY	OTHER
	Cells	Orgs.	Specimen	Bacterial Culture	Tissue Culture	Egg Inoc.	Animal Inoc.	Antibody*	
Gram-pos. cocci									
Staphylococcus	PMNs	+	CSF Blood Wound	Blood Agar (Broth)	—	—	—	—	—
Streptococcus	PMNs	+	CSF Blood Wound	Blood Agar (Broth)	—	—	—	Antistrepto-lysin	—
Pneumococcus	PMNs	+	CSF Blood ENT	Blood Agar (CO_2) (Broth)	—	—	Mice, i.p.	Opsonin Bactericidal	SSS in CSF
Gram-neg. cocci									
Meningococcus	PMNs	±	CSF Blood N & Thr.	Chocolate Agar (CO_2)	—	—	Mice, i.p. (mucin)	Bactericidal	—
N. flavescens	PMNs	±	CSF N & Thr.	Nutrient Agar	—	—	—	Aggluts.	—
Gras-pos. bacilli									
Anthrax	PMNs	+	CSF Wound	Blood Agar	—	—	Mice G. pig.	—	—
L. monocyto-gones	PMNs Lymphs	+	CSF Wound	Blood Agar	—	—	Mice Rabbit eye (local immuni-ty)	—	—
Gram-neg. bacilli									
H. influenzae	PMNs	±	CSF Blood N. & Thr.	Chocolate Agar (CO_2) Levinthal Broth	—	—	Mice, i.c.	Bactericidal	—
E. coli	PMNs	+	CSF Wound Urine	EMB Agar	—	—	—	—	—

(Continued)

TABLE 2.—Etiologic Diagnosis of Bacterial Meningitis (*Cont.*)

Bacterial Etiology	CSF Smear		Isolation of Agent					Serology	Other
	Cells	Orgs.	Specimen	Bacterial Culture	Tissue Culture	Egg Inoc.	Animal Inoc.	Antibody*	
A. Aerogenes	PMNs	+	CSF Wound Urine	EMB Agar	—	—	—	—	—
K. pneumoniae	PMNs	+	CSF Blood Sputum	EMB Agar	—	—	—	—	—
Ps. aeruginosa	PMNs	+	CSF ENT	Nutrient Agar	—	—	—	—	Pyocyanin in CSF
Proteus sp.	PMNs	+	CSF ENT Urine	Nutrient Agar	—	—	—	—	—
Salmonella sp.	PMNs or Lymphs	±	Blood Stool CSF	EMB Agar	—	—	—	Aggluts.	—
Brucella sp.	PMNs or Lymphs	±	Blood CSF	Trypticase Soy (sealed)	—	Yolk sac	—	C.F. Aggluts. (Blood & CSF)	Skin test
Pasteurella sp.	PMNs or Lymphs	±	—	—	—	—	—	—	—
Tubercle bacilli	Lymphs ± PMNs	±	CSF Sputum	Tarshis Lowenstein Dubos media	—	Yolk sac	G. pig.	Sensitized sheep RBC	Skin test biopsy
Leptospira sp.	Lymphs	Phase or Dark Field±	CSF Plasma Urine	Rabbit serum	—	Allantoic membrane	G. pig.	C.F. Aggluts. Lysis	—
Syphilis (treponeme)	Lymphs	0	—	—	—	—	—	C.F. TPI (CSF and serum)	

TABLE 3.—Etiologic Diagnosis of Viral Meningitis

							TPI (CSF and serum)	

TABLE 3.—ETIOLOGIC DIAGNOSIS OF VIRAL MENINGITIS

VIRAL ETIOLOGY	CSF SMEAR		ISOLATION OF AGENT					SEROLOGY	OTHER
	Cells	Orgs.	Specimen	Bacterial Culture	Tissue Culture	Egg Inoc.	Animal Inoc.	Antibody	
LCM	Lymphs	0	CSF Blood Stool	0	—	—	Mice, i.c. G. pig.	C.F.**—3 wks. Neut.—6 wks.	—
Mumps	Lymphs	0	CSF Saliva	0	—	Amnion	Monkey	C.F.—3 wks. HI—4-6 wks. Neut.	Skin test
Herpes simplex	Lymphs	0	CSF	0	HeLa	CAM°	Rabbit cornea Mice, i.c.	C.F.—1 wk. Neut.	—
Inf. mononucleosis	PMNs Lymphs	0	—	0	—	—	—	Heterophil (Beef rbc)	
Prim. atypical pneumonia	Lymphs	0	Sputum	0	—	—	?White cotton rat	Cold and Strep. mg. Aggluts.	
Lymphopathia venereum	Lymphs PMNs RBCs±	0	CSF Cutaneous scrapings	0	—	CAM	Mice, i.c. G. pig.	C.F.	Skin test
Cat-scratch fever	Lymphs	0	—	0	—	—	—	C.F.	Skin test
Encephalo myocarditis	Lymphs	0	CSF Blood	0	—	—	Mice, i.c.	C.F. Neut. HI	
Rubeola	Lymphs	0	Blood Throat	0	Primate kidney	Amnion	—	Neut.	
Epidemic encephalitis	Lymphs	0	CSF Blood	0	—	—	Mice, i.c.	Neut. C.F.	—
Rabies	Lymphs	0	CSF Saliva	0	Mouse brain	—	Mice, i.c.	—	Negri bodies

(*Continued*)

TABLE 3.—ETIOLOGIC DIAGNOSIS OF VIRAL MENINGITIS (*Cont.*)

VIRAL ETIOLOGY	CSF SMEAR		ISOLATION OF AGENT					SEROLOGY	OTHER
	Cells	Orgs.	Specimen	Bacterial Culture	Tissue Culture	Egg Inoc.	Animal Inoc.	Antibody	
Inf. polyneuritis	None ± Lymphs	0	—	0	—	—	—	—	—
Poliomyelitis	Lymphs PMNs	0	CSF Throat Stool	0	Monkey kidney or HeLa	—	Monkey, i.c.	C.F. Neut.	—
Coxsackie A-9	Lymphs PMNs	0	CSF Throat Stool	0	—	—	Suckling mice, i.c.	C.F.	—
Coxsackie B	Lymphs PMNs	0	CSF Throat Stool	0	Monkey kidney or HeLa	—	Suckling mice	C.F.	—
ECHO	Lymphs PMNs	0	CSF Throat Stool	0	Monkey kidney or HeLa	—	—	Neut.	
Neuromyasthenia	None	0	Stool	0	—	—	—	—	Bethesda-Ballerup (para-colon) Aggluts.
Myalgic encephalitis	Lymphs or none	0	—	0	—	—	—	—	—

*CAM = chorioallantoic membrane.
**C.F. = complement-fixing antibody.

TABLE 4.—ETIOLOGIC DIAGNOSIS OF FUNGAL MENINGITIS

TABLE 4.—ETIOLOGIC DIAGNOSIS OF FUNGAL MENINGITIS

FUNGAL ETIOLOGY	CSF SMEAR		ISOLATION OF AGENT					SEROLOGY	OTHER
	Cells	Orgs.	Specimen	Bacterial Culture	Tissue Culture	Egg Inoc.	Animal Inoc.	Antibody	
C. neoformans	Lymphs	+	CSF	Sabouraud's agar	—	—	Mice, i.p.	—	Biopsy
No. Am. Blastomyc.	Lymphs or none	+	CSF Pustule	Blood agar	—	—	—	C.F.*	Skin test
Monilia	Lymphs	+	CSF Skin	Sabouraud's agar	—	—	—	Aggluts.±	Skin test±
Nocardia	PMNs Lymphs	+	CSF Pus	Sabouraud's agar	—	—	G. pig, i.p. Rabbit i.v.	—	—
Actinomycosis	PMNs Lymphs	+	CSF Pus	BHI broth (anaerobic)	—	—	?G. pig. ?Rabbit	—	Discharge "sulfur granules"
Sporotrichum schenchii	Lymphs	+	CSF Pustule	Sabouraud's agar	—	—	—	C.F. Aggluts.	Skin test
Coccidioides	Lymphs	+	CSF Sputum Pus	Sabouraud's agar	—	—	Mice, i.p.	C.F. Precip.	Skin test

*C.F. = complement-fixing antibody.

Identification by Smear

A smear of spinal-fluid sediment or pellicle is one of the most readily available and most useful methods for determining etiology of the infection. Even in bacterial meningitis, however, it does not always show the causative microorganisms, although the bacteria can be recovered in cultures. When the organisms are seen the diploid, biscuit-shaped, gram-negative meningococcus and the coccoid-bacillary influenza bacillus may be distinctive. In pneumococcal meningitis there is often a great number of diplococci present on the smear of CSF. The gram-positive, lancet-shaped pneumococcus is characteristic and can be verified by specific capsular swelling. Clumped staphylococci and chained streptococci also can be readily recognized, and other species such as the anthrax bacillus, *Cryptococcus neoformans* and some of the fungi, are striking in their appearance in the CSF. Most gram-negative bacilli are pleomorphic, and the distinction of the species is inaccurate. Acid-fast tubercle bacilli can be identified by smear, especially in a smear of the pellicle, but they are seen in only one third to one half of patients with tuberculous meningitis.

In some bacterial and fungal causes of meningitis, the organisms may be seen in a stained smear of pus discharging from the middle ear or from cutaneous lesions, from the throat, sputum or urine.

Isolation of the Etiologic Agent

Recovery of the causative organism on semisolid medium is the principal method of identifying the specific etiology of bacterial or fungal meningitis. Of course, the cultures should be taken before treatment, whenever possible. The selection of media and conditions of culture are most important for successful isolation in some instances, whereas cultivation of other species is relatively easy. The meningococcus and *H. influenzae* both have fastidious growth requirements. The use of chocolate agar and a CO_2 atmosphere increases the frequency of successful results. It is also helpful to allow the CSF to drip directly from the needle onto a chocolate agar plate or slant.

Technics for in vitro cultivation of the tubercle bacillus have improved remarkably within recent years, and positive

cultures can be obtained from a large proportion of patients on incubation of a suitable culture for 2-6 weeks. Cultures should be taken before treatment, even though it is prudent to begin treatment of patients with tuberculous meningitis before the cultures are mature. It is possible, however, to obtain positive isolates of tubercle bacilli from CSF for several days after chemotherapy has been started.

For the most part, yeasts and fungi grow well on Sabouraud's media. Some species require attention to temperature and oxygen content of the environment in which they are grown, and the duration of incubation period is variable. Laboratory personnel should be familiar with the potential hazards of transmission from some cultures, especially in the hyphal phase.

At present, it is not common practice to attempt virus isolations from the CSF of patients with viral meningitis. As noted in Table 2, however, it is possible by proper selection of tissue culture cells, embryonated eggs or experimental animals to isolate most viruses that cause aseptic meningitis. Frequently they can be obtained from other sources than CSF. Collection and handling of specimens to be used for virus isolations require special precautions to preserve the viability of the virus. If studies are not to be initiated immediately, provisions must be made for proper storage. In epidemic outbreaks it is important to furnish specimens for virus studies to the Public Health Service or other suitable laboratories to establish the cause of the outbreak as quickly as possible. This will facilitate other diagnostic studies and assist in the management of other patients.

Serologic Diagnosis

Serologic technics are a valuable means of obtaining a definitive etiologic diagnosis in bacterial, fungal or viral meningitis. For the latter, serologic diagnosis is by far the most convenient and available. Even when isolation studies are made, it is necessary to establish a significant antibody response by serologic tests to interpret, with confidence, the etiologic role of the agent. Demonstration of the presence of antibody in a single-serum specimen is rarely diagnostic by itself. Paired serum specimens are necessary to verify an increase in antibody against the causative agent, and a serum specimen for this purpose should be obtained early in the acute phase of

the illness. The potential value of such a specimen in the serologic diagnosis of meningitis can hardly be overemphasized. The convalescent-phase specimen can be obtained from 1 week to several weeks later. As noted in Table 3, one may test for a variety of types of antibody. These include bacterial agglutinins, bactericidal antibody, precipitins, cold and heterophile agglutinins, complement fixing, hemagglutination inhibiting and neutralizing antibody. Properly collected, paired serum specimens are suitable for any of these tests, and their use is strongly recommended for accurate diagnosis of the specific etiology of meningitis, especially in cases of aseptic meningitis of viral origin.

Mixed infections, sometimes occurring in secondary purulent meningitis, should alert the physician to search for a primary lesion, if it has not been previously recognized. Apparently, mixed infections with viruses also occur as, for example, the association of some types of Coxsackie A viruses and poliomyelitis.

All causes of meningitis are not known. The optimal use of methods described in this section, however, will permit the recognition of the causative agent in 75-90% of cases of bacterial or fungal meningitis and about 50% of patients with aseptic meningitis. Antibiotic treatment decreases the likelihood of identifying the primary cause of meningitis of unknown etiology.

TREATMENT AND PREVENTION

General Principles of Management

Patients with meningitis should be hospitalized, if possible. Isolation is not required, but it is desirable for cases of meningococcal meningitis until after-treatment has been initiated. It also is wise to isolate patients with meningitis of unknown etiology during their acute illness. The urgency for treatment varies greatly among patients. Except for those with fulminating meningococcemia, there is ample time for hospital admission, careful clinical examination of the patient, lumbar puncture and the initial laboratory procedures that assist in establishing a complete diagnosis. General supportive measures include treatment of shock, maintenance of adequate respiration and relief of hyperpyrexia. Sedation seldom is necessary, and narcotics should be avoided. In patients with

bacterial meningitis, specific treatment should be initiated as soon as possible.

Specific antimicrobial agents are, for the most part, administered systemically, and a parenteral route is considered preferable during the first few days of treatment. Large doses must be given. Concentration of various antibiotics and chemotherapeutic agents in the brain and CSF is often low compared with the plasma concentration, because of so-called blood-brain-CSF barrier. The degree to which different antibiotics enter the brain parenchyma and CSF from the plasma is variable, but a ratio of about 1:10 is common, whereas one can expect sulfonamides to attain equilibrium between the CSF and plasma. Acute inflammation increases the diffusion through the meninges. In the treatment of meningitis, the necessity for an antibacterial concentration of drug in the CSF has been questioned. Nevertheless, it is considered the best available indication of the adequacy of drug therapy.

Some antibiotics cannot be given in adequate doses to enter the CSF by the systemic route without producing excessive toxicity. These include streptomycin, neomycin, polymyxin and bacitracin, which can be useful, even lifesaving, in certain types of meningitis. All these agents have been administered locally into the cerebrospinal cavity. In the proper dosage, the immediate toxicity by this route is acceptable, if their use is essential. The chronic effects among most patients who recover are minimal, but occasionally they are significantly adverse.

In treating subacute and chronic meningitis in which a cerebrospinal block has occurred or is known to be a common complication, the intrathecal injection of proteolytic enzymes or staphylokinase with and without plasminogen has been used. The benefit of these procedures is equivocal. Also, streptodornase and other nonantimicrobial agents have been injected into the subarachnoid space in certain types of meningitis, without conclusive improvement.

The administration of adrenal corticosteroids can be considered specific therapy in meningococcic meningitis with involvement of the adrenals. Intravenous administration of hydrocortisone is indicated. No specific indication for adrenal corticosteroids exists in other forms of meningitis. Their use has been recommended, however, as a means of reducing intracranial inflammation, diminishing the likelihood of cerebrospinal block and as an adjunct in the control of hyper-

pyrexia. There is little question that such use is unnecessary and of doubtful benefit in all but extreme cases. In the latter group, their value has been statistically insignificant.

In addition to the general supportive measures and specific antimicrobial treatment, certain neurosurgical procedures also have a place in the management of patients with meningitis. Drainage of localized pus and relief from excessive intracranial pressure in chronic forms of meningitis are the principal indications for surgery in these patients.

Treatment of Meningitis of Known Etiology

Bacterial meningitis.—In large series of patients, the case fatality from bacterial meningitis other than tuberculous ranges from 5 to 35%. More than one half of deaths in the pediatric age group are in patients under 1 year of age, with an especially high fatality rate in the neonatal period. Among adults, most deaths are after age 40. The over-all case fatality among patients infected with *H. influenzae*, meningococcus or pneumococcus is between 3 and 15%, whereas that with gram-negative bacilli is still about 50%, and staphylococcal meningitis is fatal in approximately 70% of cases. Residual abnormalities can be expected in 10% of pneumococcal infections, about 6% of meningococcal meningitis and a smaller percentage of infections with *H. influenzae*.

Meningococcal meningitis can be treated effectively with several antibacterial agents. A sulfonamide is the drug of choice. Sulfadiazine has been used most extensively, although newer preparations may be acceptable. An initial loading dose should be given, parenterally. In adults 4.0-6.0 Gm. of sulfadiazine is recommended and 100 mg./kg. for children. A maintenance dose of 1.0 Gm. every 4-6 hours, and 30 mg./kg. in children, can be given either orally or parenterally. Medication should be continued 5 days beyond the remission of fever. The hydration of the patient requires attention, to avoid renal toxicity from the drug.

Penicillin in doses of one million units intramuscularly every 2 hours is a suitable alternative treatment. Also tetracycline, 50 mg./kg. may be given intravenously as an initial dose and repeated daily in divided doses at 6-hour intervals. Chloramphenicol, 50-75 mg./kg./day intravenously is effective treatment.

Family members and other close contacts of patients with

meningococcal meningitis should receive sulfonamide, to eliminate the potential meningococcic carrier state (37). Treatment should be simultaneous for 1-3 days, with a dose of 1.0-2.0 Gm. of sulfadiazine daily.

INFLUENZAL MENINGITIS can be treated effectively by tetracycline or chloramphenicol in the doses mentioned. The latter also may be given at 6-hour intervals as intramuscular injections. Sulfonamides have an effect on this organism, but the results are inferior to those obtained with the preceding agents, and their use in combination does not contribute significantly, if adequate doses of tetracycline or chloramphenicol are given. Penicillin is not selected knowingly for treatment, but both in vitro studies and some chance cases have shown it to be effective in large doses.

PNEUMOCOCCAL MENINGITIS can be treated most effectively with penicillin. Intramuscular doses of one million units of aqueous crystalline potassium or sodium salt of penicillin G every 2 hours is usually sufficient. Intrathecal therapy is not necessary. Benemid®, 40 mg./kg./day to a total of 2.0 Gm., given by mouth, will aid in maintaining a higher and more constant penicillinemia, but its use is not required in most cases. Tetracycline is less bactericidal, yet in doses of 50 mg./kg./day is generally effective treatment, if penicillin cannot be used. It should not be given in combination with penicillin. Erythromycin, 50 mg./kg./day, is about as effective as tetracycline. Sulfonamides and chloramphenicol are not recommended as drugs of primary usefulness in this infection, and their addition to the therapeutic regimen is of doubtful benefit.

Infections with streptococci can be treated in the manner recommended for pneumococci. Staphylococcal meningitis is seldom responsive to penicillin. A combination of erythromycin with chloramphenicol or tetracycline is preferred as the initial therapy. Novobiocin, vancomycin or ristocetin may be useful. Systemic and intrathecal bacitracin have been effective last-choice measures.

MENINGITIS DUE TO GRAM-NEGATIVE BACILLI is most effectively treated with intravenous tetracycline or chloramphenicol. The principal exception is *Ps. aeruginosa* for which polymyxin B, 2 mg./kg./day intramuscularly and 5-10 mg./day intrathecally is the treatment most likely to be successful. Because of the tendency to relapse, gram-negative infections should be treated for 10 days after defervescence.

TUBERCULOUS MENINGITIS.—Treatment of tuberculous meningitis and, concomitantly, prognosis have changed rapidly within recent years, although there is still a significant case fatality rate. Under the regimens to be described, 25-75% of patients survive and of these only about one fifth have relapses or significant sequelae. Isonicotinic acid hydrazide (INH), 10-20 mg./kg./day, should always be included in treatment. It can be given by the oral or parenteral route. Although the data are controversial, recent evidence suggests that 20 mg./kg. is better than the usual dose of 10 mg./kg. at least for the first 30 days of treatment. A maintenance dose of 5-10 mg./kg. seems satisfactory. Intraspinal inoculation is not necessary or desirable. Minor toxic manifestations from the drug have been observed in as many as 25%, but rarely require discontinuation of treatment.

Tradition and theoretical knowledge dictate that a second antituberculous drug should always be given with INH, and some workers are strong proponents of simultaneous treatment with 3 drugs. In controlled clinical investigations, the benefit from a second drug is difficult to discern, and the value of the third agent entirely inapparent. At present, we favor the use of 2 drugs for the treatment of tuberculous meningitis. INH may be supplemented by intramuscular SM, 1.0 Gm. 2 or 3 times weekly, or by para-amino salicylic acid (PAS) in increasing dosage, as tolerated, up to 15.0 Gm. daily by mouth, or parenterally if necessary. The subarachnoid injection of SM causes an increased frequency of complications and does not add significantly to the survival rate. Also, the intrathecal injection of tuberculin which has been recommended by some authors is accompanied by complications and its benefits are nebulous.

Patients who have received less than 30 days' treatment almost invariably die of the disease, usually within a few months. Four weeks are considered minimal for hospital treatment and 1-2 years, minimal duration of continuous treatment. Pyridoxine, vitamin B_6, 25-100 mg. daily has been shown to diminish peripheral neuritis induced by INH (38).

Small numbers of cases in different series seem to have shown improvement by the simultaneous administration of cortisone or prednisone for a few days to a few weeks with the antituberculous drugs. The principal claim is that it pre-

vents or relieves cerebrospinal fluid blockage. In other series, its beneficial effects have been obscure.

Surgical relief of excessive intracranial pressure can at times prolong life and provide the time necessary for drug therapy to become effective. If available, neurosurgical consultation should be obtained when patients manifest a progressive rise in intracranial pressure.

Prevention of meningitis can be accomplished by the recognition and evaluation of primary tuberculous infections in children, early treatment of miliary tuberculosis and effective control of active focal tuberculosis. With rare exception, no cases of tuberculous meningitis have developed during treatment with INH.

SYPHILITIC MENINGITIS.—Penicillin has proved to be a highly effective drug for the treatment of syphilitic meningitis. A total dosage of 6-12 million units is required over a period of at least 10 days (39). If penicillin cannot be used, tetracycline also is effective.

FUNGAL MENINGITIS.—Many chemical and antibiotic substances have been recommended for the treatment of systemic mycoses. These include some which, in particular types of infection, seem to be effective, such as iodides, sulfonamides, stilbamidines, penicillin, tetracycline, mycostatin and amphotericin. At present one can offer no effective treatment for Cryptococcus meningitis. Amphotericin B given parenterally and large doses of sulfonamide have given the most favorable results (40). Other fungal infections of the meninges also are treated with difficulty and usually require long-term therapy. Meningitis caused by nocardia or actinomyces can be treated with success by tetracycline and with lesser effect by penicillin or sulfonamides. The intravenous administration of 2-hydroxystilbamidine in a dose of 50-150 mg. daily is recommended for blastomycosis.

VIRAL MENINGITIS.—Treatment of viral meningitis at present is entirely supportive. No specific antiviral drugs are available for treating human beings, with the exception of tetracycline, which inhibits psittacosis. Otherwise the administration of antibiotics does not shorten or ameliorate the course of viral meningitis.

TREATMENT OF MENINGITIS OF UNKNOWN ETIOLOGY

The rapid pathologic progression of acute purulent meningitis and the availability of effective antibacterial agents some-

times make it necessary to begin treatment without definite knowledge concerning the specific etiology of the infection. In the selection of therapy, it is desirable to provide a regimen that will be effective against the most probable organism on the basis of clinical findings and at the same time provide sufficient latitude for clinical error. No single regimen is entirely satisfactory under these conditions. One can make a recommendation on a statistical and empiric basis because of the frequency of different kinds of meningitis in patients of different ages. Thus, among young children, tetracycline or chloramphenicol is suggested in the doses previously recommended. If at all possible, treatment should be initiated with parenteral administration of the drug. Among adolescents and adults, treatment with large doses of aqueous crystalline penicillin is preferred. Either regimen is likely to fail in patients infected with resistant staphylococci. If findings suggest staphylococcal infection, treatment should be directed specifically at its control. In any case, the administration of several drugs in an attempt to cover the entire front is unnecessary, for it introduces complications and difficulties in drug administration, especially if drugs are given in the individually effective doses, as they should be. These recommendations using an adequate dose of a single or, occasionally, 2 drugs have been found to be workable and effective in most cases in which the etiology of purulent meningitis is unknown. Treatment of aseptic meningitis is rarely necessary in the absence of an etiologic diagnosis.

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